Avoid taking with >10/20 mg VYTORIN (or 10/40 mg for patients who have previously taken 80 mg simvastatin chronically, e.g., for 12 months or more, without evidence of muscle toxicity), based on clinical experience					
Lomitapide	60 mg QD for 7 days	40 mg single dose	simvastatin acid simvastatin	1.7 2	1.6 2
Lomitapide	10 mg QD for 7 days	20 mg single dose	simvastatin acid simvastatin	1.4 1.6	1.4 1.7
No dosing adjustments required for the following:					
Fenofibrate	160 mg QD for 14 days	80 mg QD on Days 8-14	simvastatin acid simvastatin	0.64 0.89	0.89 0.83
Propranolol	80 mg single dose	80 mg single dose	total inhibitor active inhibitor	0.79 0.79	↓ from 33.6 to 21.1 ng·eq/mL ↓ from 7.0 to 4.7 ng·eq/mL

* Results based on a chemical assay except results with propranolol as indicated.
† Results could be representative of the following CYP3A4 inhibitors: ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone.
‡ Simvastatin acid refers to the β-hydroxyacid of simvastatin.
§ The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.
¶ Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose simvastatin and 30 and 90 minutes following single dose simvastatin on Day 3.
# Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and simvastatin was administered in the evening on Day 3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VYTORIN

No animal carcinogenicity or fertility studies have been conducted with the combination of ezetimibe and simvastatin. The combination of ezetimibe with simvastatin did not show evidence of mutagenicity *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with ezetimibe and simvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin (1:1) in the *in vivo* mouse micronucleus test.

Ezetimibe

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe).

Simvastatin

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively, (as total inhibitory activity based on AUC) after an

80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80-mg daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

13.2 Animal Toxicology and/or Pharmacology

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

Ezetimibe

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED_{50} value of 0.5 μg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED_{50} values in dogs, rats, and mice were 7, 30, and 700 μg/kg/day, respectively. These results are consistent with ezetimibe being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (ezetimibe-glucuronide) was administered intraduodenally, the metabolite was as potent as ezetimibe in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03 to 300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of ^{14}C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat-soluble vitamins A and D.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug-metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with statins (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

VYTORIN

VYTORIN reduces total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C in patients with hyperlipidemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

VYTORIN is effective in men and women with hyperlipidemia. Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of VYTORIN.

Five multicenter, double-blind studies conducted with either VYTORIN or coadministered ezetimibe and simvastatin equivalent to VYTORIN in patients with primary hyperlipidemia are reported: two were comparisons with simvastatin, two were comparisons with atorvastatin, and one was a comparison with rosuvastatin.

In a multicenter, double-blind, placebo-controlled, 12-week trial, 1528 hyperlipidemic patients were randomized to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or VYTORIN (10/10, 10/20, 10/40, or 10/80).

When patients receiving VYTORIN were compared to those receiving all doses of simvastatin, VYTORIN significantly lowered total-C, LDL-C, Apo B, TG, and non-HDL-C. The effects of VYTORIN on HDL-C were similar to the effects seen with simvastatin. Further analysis showed VYTORIN significantly increased HDL-C compared with placebo. (See Table 7.) The lipid response to VYTORIN was similar in patients with TG levels greater than or less than 200 mg/dL.

Table 7: Response to VYTORIN in Patients with Primary Hyperlipidemia (Mean* % Change from Untreated Baseline†)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG*	Non-HDL-C
Pooled data (All VYTORIN doses)‡	609	-38	-53	-42	+7	-24	-49
Pooled data (All simvastatin doses)‡	622	-28	-39	-32	+7	-21	-36
Ezetimibe 10 mg	149	-13	-19	-15	+5	-11	-18
Placebo	148	-1	-2	0	0	-2	-2
VYTORIN by dose							
10/10	152	-31	-45	-35	+8	-23	-41
10/20	156	-36	-52	-41	+10	-24	-47
10/40	147	-39	-55	-44	+6	-23	-51
10/80	154	-43	-60	-49	+6	-31	-56
Simvastatin by dose							
10 mg	158	-23	-33	-26	+5	-17	-30
20 mg	150	-24	-34	-28	+7	-18	-32
40 mg	156	-29	-41	-33	+8	-21	-38
80 mg	158	-35	-49	-39	+7	-27	-45

* For triglycerides, median % change from baseline.
† Baseline - on no lipid-lowering drug.
‡ VYTORIN doses pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, and non-HDL-C compared to simvastatin and significantly increased HDL-C compared to placebo.

In a multicenter, double-blind, controlled, 23-week study, 710 patients with known CHD or CHD risk equivalents, as defined by the NCEP ATP III guidelines, and an LDL-C ≥130 mg/dL were randomized to one of four treatment groups: coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10, 10/20, and 10/40) or simvastatin 20 mg. Patients not reaching an LDL-C <100 mg/dL had their simvastatin dose titrated at 6-week intervals to a maximal dose of 80 mg.

At Week 5, the LDL-C reductions with VYTORIN 10/10, 10/20, or 10/40 were significantly larger than with simvastatin 20 mg (see Table 8).

Table 8: Response to VYTORIN after 5 Weeks in Patients with CHD or CHD Risk Equivalents and an LDL-C ≥130 mg/dL

	Simvastatin 20 mg	VYTORIN 10/10	VYTORIN 10/20	VYTORIN 10/40
N	253	251	109	97
Mean baseline LDL-C	174	165	167	171
Percent change LDL-C	-38	-47	-53	-59

In a multicenter, double-blind, 6-week study, 1902 patients with primary hyperlipidemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of eight treatment groups: VYTORIN (10/10, 10/20, 10/40, or 10/80) or atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg).

Across the dosage range, when patients receiving VYTORIN were compared to those receiving milligram-equivalent statin doses of atorvastatin, VYTORIN lowered total-C, LDL-C, Apo B, and non-HDL-C significantly more than atorvastatin. Only the 10/40 mg and 10/80 mg VYTORIN doses increased HDL-C significantly more than the corresponding milligram-equivalent statin dose of atorvastatin. The effects of VYTORIN on TG were similar to the effects seen with atorvastatin. (See Table 9.)

Table 9: Response to VYTORIN and Atorvastatin in Patients with Primary Hyperlipidemia (Mean* % Change from Untreated Baseline†)

Treatment (Daily Dose)	N	Total-C‡	LDL-C‡	Apo B‡	HDL-C	TG*	Non-HDL-C‡
VYTORIN by dose							
10/10	230	-34§	-47§	-37§	+8	-26	-43§
10/20	233	-37§	-51§	-40§	+7	-25	-46§
10/40	236	-41§	-57§	-46§	+9§	-27	-52§
10/80	224	-43§	-59§	-48§	+8§	-31	-54§
Atorvastatin by dose							
10 mg	235	-27	-36	-31	+7	-21	-34
20 mg	230	-32	-44	-37	+5	-25	-41
40 mg	232	-36	-48	-40	+4	-24	-45
80 mg	230	-40	-53	-44	+1	-32	-50

* For triglycerides, median % change from baseline.
† Baseline - on no lipid-lowering drug.
‡ VYTORIN doses pooled (10/10-10/80) provided significantly greater reductions in total-C, LDL-C, Apo B, and non-HDL-C compared to atorvastatin doses pooled (10-80).
§ $p<0.05$ for difference with atorvastatin at equal mg doses of the simvastatin component.

In a multicenter, double-blind, 24-week, forced-titration study, 788 patients with primary hyperlipidemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to receive coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10 and 10/20) or atorvastatin 10 mg. For all three treatment groups, the dose of the statin was titrated at 6-week intervals to 80 mg. At each pre-specified dose comparison, VYTORIN lowered LDL-C to a greater degree than atorvastatin (see Table 10).

Table 10: Response to VYTORIN and Atorvastatin in Patients with Primary Hyperlipidemia (Mean* % Change from Untreated Baseline†)

Treatment	N	Total-C	LDL-C	Apo B	HDL-C	TG*	Non-HDL-C
Week 6							
Atorvastatin 10 mg‡	262	-28	-37	-32	+5	-23	-35
VYTORIN 10/10§	263	-34¶	-46¶	-38¶	+8¶	-26	-43¶
VYTORIN 10/20#	263	-36¶	-50¶	-41¶	+10¶	-25	-46¶
Week 12							
Atorvastatin 20 mg	246	-33	-44	-38	+7	-28	-42
VYTORIN 10/20	250	-37¶	-50¶	-41¶	+9	-28	-46¶
VYTORIN 10/40	252	-39¶	-54¶	-45¶	+12¶	-31	-50¶
Week 18							
Atorvastatin 40 mg	237	-37	-49	-42	+8	-31	-47
VYTORIN 10/40Þ	482	-40¶	-56¶	-45¶	+11¶	-32	-52¶
Week 24							
Atorvastatin 80 mg	228	-40	-53	-45	+6	-35	-50
VYTORIN 10/80Þ	459	-43¶	-59¶	-49¶	+12¶	-35	-55¶

* For triglycerides, median % change from baseline.
† Baseline - on no lipid-lowering drug.
‡ Atorvastatin: 10 mg start dose titrated to 20 mg, 40 mg, and 80 mg through Weeks 6, 12, 18, and 24.
§ VYTORIN: 10/10 start dose titrated to 10/20, 10/40, and 10/80 through Weeks 6, 12, 18, and 24.
¶ $p \leq 0.05$ for difference with atorvastatin in the specified week.
# VYTORIN: 10/20 start dose titrated to 10/40, 10/40, and 10/80 through Weeks 6, 12, 18, and 24.
Þ Data pooled for common doses of VYTORIN at Weeks 18 and 24.

In a multicenter, double-blind, 6-week study, 2959 patients with primary hyperlipidemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of six treatment groups: VYTORIN (10/20, 10/40, or 10/80) or rosuvastatin (10 mg, 20 mg, or 40 mg).

The effects of VYTORIN and rosuvastatin on total-C, LDL-C, Apo B, TG, non-HDL-C and HDL-C are shown in Table 11.

Table 11: Response to VYTORIN and Rosuvastatin in Patients with Primary Hyperlipidemia (Mean* % Change from Untreated Baseline†)

Treatment (Daily Dose)	N	Total-C‡	LDL-C‡	Apo B‡	HDL-C	TG*	Non-HDL-C‡
VYTORIN by dose							
10/20	476	-37§	-52§	-42§	+7	-23§	-47§
10/40	477	-39¶	-55¶	-44¶	+8	-27	-50¶
10/80	474	-44#	-61#	-50#	+8	-30#	-56#
Rosuvastatin by dose							
10 mg	475	-32	-46	-37	+7	-20	-42
20 mg	478	-37	-52	-43	+8	-26	-48
40 mg	475	-41	-57	-47	+8	-28	-52

* For triglycerides, median % change from baseline.
† Baseline - on no lipid-lowering drug.
‡ VYTORIN doses pooled (10/20-10/80) provided significantly greater reductions in total-C, LDL-C, Apo B, and non-HDL-C compared to rosuvastatin doses pooled (10-40 mg).
§ p<0.05 vs. rosuvastatin 10 mg.
¶ p<0.05 vs. rosuvastatin 20 mg.
# p<0.05 vs. rosuvastatin 40 mg.

In a multicenter, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks were randomized to receive either simvastatin 40 mg or the coadministered active ingredients equivalent to VYTORIN 10/20. The median LDL-C and HbA1c levels at baseline were 89 mg/dL and 7.1%, respectively.

VYTORIN 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg. The median percent changes from baseline for VYTORIN vs. simvastatin were: LDL-C -25% and -5%; total-C -16% and -5%; Apo B -19% and -5%; and non-HDL-C -23% and -5%. Results for HDL-C and TG between the two treatment groups were not significantly different.

Ezetimibe

In two multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hyperlipidemia, ezetimibe significantly lowered total-C (-13%), LDL-C (-19%), Apo B (-14%), and TG (-8%), and increased HDL-C (+3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

Simvastatin

In two large, placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (N=4,444 patients) and the Heart Protection Study (N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths; the risk of non-fatal myocardial infarction and stroke; and the need for coronary and non-coronary revascularization procedures.

No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

14.2 Homozygous Familial Hypercholesterolemia (HoFH)

A double-blind, randomized, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analyzed from a subgroup of patients (n=14) receiving simvastatin 40 mg at baseline. Increasing the dose of simvastatin from 40 to 80 mg (n=5) produced a reduction of LDL-C of 13% from baseline on simvastatin 40 mg. Coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/40 and 10/80 pooled, n=9), produced a reduction of LDL-C of 23% from baseline on simvastatin 40 mg. In those patients coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/80, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.

14.3 Chronic Kidney Disease (CKD)

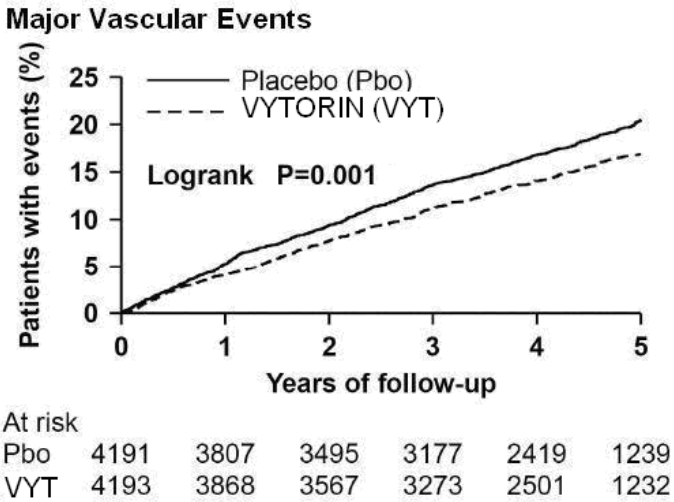
The Study of Heart and Renal Protection (SHARP) was a multinational, randomized, placebo-controlled, double-blind trial that investigated the effect of VYTORIN on the time to a first major vascular event (MVE) among 9438 patients with moderate to severe chronic kidney disease (approximately one-third on dialysis at baseline) who did not have a history of myocardial infarction or coronary revascularization. An MVE was defined as nonfatal MI, cardiac death, stroke, or any revascularization procedure. Patients were allocated to treatment using a method that took into account the distribution of 8 important baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups.

For the first year, 9438 patients were allocated 4:4:1, to VYTORIN 10/20, placebo, or simvastatin 20 mg daily, respectively. The 1-year simvastatin arm enabled the comparison of VYTORIN to simvastatin with regard to safety and effect on lipid levels. At 1 year the simvastatin-only arm was re-allocated 1:1 to VYTORIN 10/20 or placebo. A total of 9270 patients were ever allocated to VYTORIN 10/20 (n=4650) or placebo (n=4620) during the trial. The median follow-up duration was 4.9 years. Patients had a mean age of 61 years; 63% were male, 72% were Caucasian, and 23% were diabetic; and, for those not on dialysis at baseline, the median serum creatinine was 2.5 mg/dL and the median estimated glomerular filtration rate (eGFR) was 25.6 mL/min/1.73 m^2, with 94% of patients having an eGFR < 45 mL/min/1.73m^2. Eligibility did not depend on lipid levels. Mean LDL-C at baseline was 108 mg/dL. At 1 year, the mean LDL-C was 26% lower in the simvastatin arm and 38% lower in the VYTORIN arm relative to placebo. At the midpoint of the study (2.5 years), the mean LDL-C was 32% lower for VYTORIN relative to placebo. Patients no longer taking study medication were included in all lipid measurements.

In the primary intent-to-treat analysis, 639 (15.2%) of 4193 patients initially allocated to VYTORIN and 749 (17.9%) of 4191 patients initially allocated to placebo experienced an MVE. This corresponded to a relative risk reduction of 16% (p=0.001) (see Figure 1). Similarly, 526 (11.3%) of 4650 patients ever allocated to VYTORIN and 619 (13.4%) of 4620 patients ever allocated to placebo experienced a major atherosclerotic event (MAE; a subset of the MVE composite that excluded non-coronary cardiac deaths and hemorrhagic stroke), corresponding to a relative risk reduction of 17% (p=0.002). The trial demonstrated that treatment with VYTORIN 10/20 mg versus placebo reduced the risk for MVE and MAE in this CKD population. The study design precluded drawing conclusions regarding the independent contribution of either ezetimibe or simvastatin to the observed effect.

The treatment effect of VYTORIN on MVE was attenuated among patients on dialysis at baseline compared with those not on dialysis at baseline. Among 3023 patients on dialysis at baseline, VYTORIN reduced the risk of MVE by 6% (RR 0.94: 95% CI 0.80-1.09) compared with 22% (RR 0.78: 95% CI 0.69-0.89) among 6247 patients not on dialysis at baseline (interaction P=0.08).

Figure 1: Effect of VYTORIN on the Primary Endpoint of Risk of Major Vascular Events



The individual components of MVE in all patients ever allocated to VYTORIN or placebo are presented in Table 12.

Table 12: Number of First Events for Each Component of the Major Vascular Event Composite Endpoint in SHARP*

Outcome	VYTORIN 10/20 (N=4650)	Placebo (N=4620)	Risk Ratio (95% CI)	P-value
Major Vascular Events	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.001
Nonfatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-hemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Hemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularization	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.004

*Intention-to-treat analysis on all SHARP patients ever allocated to VYTORIN or placebo.

Among patients not on dialysis at baseline, VYTORIN did not reduce the risk of progressing to end-stage renal disease compared with placebo (RR 0.97: 95% CI 0.89-1.05).

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3873 — Tablets VYTORIN 10/10 are white to off-white capsule-shaped tablets with code “311” on one side.

They are supplied as follows:

NDC 66582-311-31 bottles of 30

NDC 66582-311-54 bottles of 90

NDC 66582-311-87 bottles of 10,000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

No. 3874 — Tablets VYTORIN 10/20 are white to off-white capsule-shaped tablets with code “312” on one side.

They are supplied as follows:

NDC 66582-312-31 bottles of 30

NDC 66582-312-54 bottles of 90

No. 3875 — Tablets VYTORIN 10/40 are white to off-white capsule-shaped tablets with code “313” on one side.

They are supplied as follows:

NDC 66582-313-31 bottles of 30

NDC 66582-313-54 bottles of 90

No. 3876 — Tablets VYTORIN 10/80 are white to off-white capsule-shaped tablets with code “315” on one side.

They are supplied as follows:

NDC 66582-315-31 bottles of 30

NDC 66582-315-54 bottles of 90

Storage

Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Keep container tightly closed.

Storage of 10,000, 5000, and 2500 count bottles

Store bottle of 10,000 VYTORIN 10/10 and 10/20, 5000 VYTORIN 10/40, and 2500 VYTORIN 10/80 capsule-shaped tablets at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Store in original container until time of use. When product container is subdivided, repackage into a tightly-closed, light-resistant container. Entire contents must be repackaged immediately upon opening.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

Patients should be advised about substances they should not take concomitantly with VYTORIN *[see Contraindications (4) and Warnings and Precautions (5.1)]*. Patients should also be advised to inform other healthcare professionals prescribing a new medication or increasing the dose of an existing medication that they are taking VYTORIN.

17.1 Muscle Pain

All patients starting therapy with VYTORIN should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing VYTORIN. **Patients using the 10/80-mg dose should be informed that the risk of myopathy, including rhabdomyolysis, is increased with the use of the 10/80-mg dose.** The risk of myopathy, including rhabdomyolysis, occurring with use of VYTORIN is increased when taking certain types of medication or consuming grapefruit juice. Patients should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes

It is recommended that liver function tests be performed before the initiation of VYTORIN, and thereafter when clinically indicated. All patients treated with VYTORIN should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using VYTORIN. Discuss future pregnancy plans with your patients, and discuss when to stop taking VYTORIN if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking VYTORIN and call their healthcare professional.

17.4 Breastfeeding

Women who are breastfeeding should be advised to not use VYTORIN. Patients who have a lipid disorder and are breastfeeding should be advised to discuss the options with their healthcare professional.

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For patent information: www.merck.com/product/patent/home.html

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Patient Information

VYTORIN® (VI-tor-in)

(ezetimibe and simvastatin)

Tablets

Read this Patient Information carefully before you start taking VYTORIN® and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about VYTORIN, ask your doctor. Only your doctor can determine if VYTORIN is right for you.

What is VYTORIN?

VYTORIN is a prescription medicine that contains 2 cholesterol lowering medicines, ezetimibe and simvastatin. VYTORIN is used along with diet to:

- lower the level of your "bad" cholesterol (LDL)
- increase the level of your "good" cholesterol (HDL)
- lower the level of fat in your blood (triglycerides)

VYTORIN is for patients who cannot control their cholesterol levels by diet and exercise alone.
VYTORIN has not been shown to reduce heart attacks or strokes more than simvastatin alone.

It is not known if VYTORIN is safe and effective in children under 10 years of age or in girls who have not started their period (menses).

The usual dose of VYTORIN is 10/10 mg to 10/40 mg 1 time each day.

VYTORIN 10/80 mg increases your chance of developing muscle damage. The 10/80 mg dose should only be used by people who:

- have been taking VYTORIN 10/80 mg chronically (such as 12 months or more) without having muscle damage
- do not need to take certain other medicines with VYTORIN that would increase your chance of getting muscle damage.

If you are unable to reach your LDL-cholesterol goal using VYTORIN 10/40 mg, your doctor should switch you to another cholesterol-lowering medicine.

Who should not take VYTORIN?

Do not take VYTORIN if you take:

- Certain anti-fungal medicines including:
  - itraconazole
  - ketoconazole
  - posaconazole

- voriconazole

- HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir, tipranavir, or atazanavir)
- Certain hepatitis C virus protease inhibitors (such as boceprevir or telaprevir)
- Certain antibiotics, including:
  - erythromycin
  - clarithromycin
  - telithromycin
- nefazodone
- medicines containing cobicistat
- A fibric acid medicine for lowering cholesterol called gemfibrozil
- cyclosporine
- danazol

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Also do not take VYTORIN if you:

- are allergic to ezetimibe or simvastatin or any of the ingredients in VYTORIN. See the end of this leaflet for a complete list of ingredients in VYTORIN.
- have liver problems.
- are pregnant or plan to become pregnant. VYTORIN may harm your unborn baby. If you are a woman of childbearing age, you should use an effective method of birth control to prevent pregnancy while using VYTORIN. If you become pregnant while taking VYTORIN, stop taking VYTORIN and call your doctor.
- are breastfeeding or plan to breastfeed. It is not known if VYTORIN passes into your breast milk. You and your doctor should decide the best way to feed your baby if you take VYTORIN.

What should I tell my doctor before and while taking VYTORIN?

Tell your doctor if you:

- have unexplained muscle aches or weakness
- have kidney problems
- have or have had liver problems or drink more than 2 glasses of alcohol daily
- have thyroid problems
- are 65 years of age or older
- are Chinese

Also see “What are the possible side effects of VYTORIN?”

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Tell your doctor who prescribes VYTORIN if another doctor increases the dose of another medicine you are taking.

Talk to your doctor before you start taking any new medicines.

Taking VYTORIN with certain other medicines may affect each other causing side effects. VYTORIN may affect the way other medicines work, and other medicines may affect how VYTORIN works.

Taking VYTORIN with certain substances can increase the risk of muscle problems. It is especially important to tell your doctor if you take:

- fibric acid derivatives (such as fenofibrate)
- amiodarone or dronedarone (drugs used to treat an irregular heartbeat)
- verapamil, diltiazem, amlodipine, or ranolazine (drugs used to treat high blood pressure, chest pain associated with heart disease, or other heart conditions)
- grapefruit juice (which should be avoided while taking VYTORIN)
- colchicine (a medicine used to treat gout)
- lomitapide (a medicine used to treat a serious and rare genetic cholesterol condition)
- daptomycin (a drug used to treat complicated skin and bloodstream infections)
- large doses of niacin or nicotinic acid

Tell your doctor if you are taking niacin or a niacin-containing product, as this may increase your risk of muscle problems, especially if you are Chinese.

It is also important to tell your doctor if you are taking coumarin anticoagulants (drugs that prevent blood clots, such as warfarin).

Tell your doctor about all the medicines you take, including any prescription and nonprescription medicines, vitamins, and herbal supplements.

How should I take VYTORIN?

- Take VYTORIN exactly as your doctor tells you to take it.
- Do not change your dose or stop taking VYTORIN without talking to your doctor.
- Take VYTORIN 1 time each day in the evening.
- Take VYTORIN with or without food.
- While taking VYTORIN, continue to follow your cholesterol-lowering diet and to exercise as your doctor told you to.
- If you miss a dose, do not take an extra dose. Just resume your usual schedule.
- Your doctor should do fasting blood tests to check your cholesterol while you take VYTORIN. Your doctor may change your dose of VYTORIN if needed.
- If you take too much VYTORIN, call your doctor or Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of VYTORIN?

VYTORIN may cause serious side effects, including:

- **Muscle pain, tenderness and weakness (myopathy).** Muscle problems, including muscle breakdown, can be serious in some people and rarely cause kidney damage that can lead to death.

Tell your doctor right away if:

- **you have unexplained muscle pain, tenderness, or weakness, especially if you have a fever or feel more tired than usual, while you take VYTORIN.**
- you have muscle problems that do not go away even after your doctor has advised you to stop taking VYTORIN. Your doctor may do further tests to diagnose the cause of your muscle problems.

Your chances of getting muscle problems are higher if you:

- are taking certain other medicines while you take VYTORIN
- are 65 years of age or older
- are female
- have thyroid problems (hypothyroidism) that are not controlled
- have kidney problems
- are taking higher doses of VYTORIN, particularly the 10/80 mg dose
- are Chinese

- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking VYTORIN and if you have any symptoms of liver problems while you take VYTORIN. Call your doctor right away if you have the following symptoms of liver problems:
  - loss of appetite
  - upper belly pain
  - dark urine
  - yellowing of your skin or the whites of your eyes
  - feel tired or weak

The most common side effects of VYTORIN include:

- headache
- increased liver enzyme levels
- muscle pain
- upper respiratory infection
- diarrhea

Additional side effects that have been reported in general use with VYTORIN or with ezetimibe or simvastatin tablets (tablets that contain the active ingredients of VYTORIN) include:

- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (which may require treatment right away), rash, hives; joint pain; inflammation of the pancreas; nausea; dizziness; tingling sensation; depression; gallstones; trouble sleeping; poor memory; memory loss; confusion; erectile dysfunction; breathing problems including persistent cough and/or shortness of breath or fever.

Tell your doctor if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of VYTORIN. For more information, ask your doctor or pharmacist.

Call your doctor about medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VYTORIN?

- Store VYTORIN at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep VYTORIN in its original container until you use it.
- Keep VYTORIN in a tightly closed container, and keep VYTORIN out of light.

Keep VYTORIN and all medicines out of the reach of children.

General Information about the safe and effective use of VYTORIN.

VYTORIN works to reduce your cholesterol in two ways. It reduces the cholesterol absorbed in your digestive tract, as well as the cholesterol your body makes by itself. VYTORIN does not help you lose weight.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VYTORIN for a condition for which it was not prescribed. Do not give VYTORIN to other people, even if they have the same condition that you have. It may harm them.

This Patient Information summarizes the most important information about VYTORIN. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about VYTORIN that is written for health professionals.

For more information, go to www.VYTORIN.com, or call 1-800-672-6372.

What are the ingredients in VYTORIN?

Active Ingredients: ezetimibe and simvastatin

Inactive Ingredients: butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hypromellose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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